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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/651,136	08/28/2003	Sandor Sipka	22740-2	8175

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EXAMINER	
ROONEY, NORA MAUREEN	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,136	SIPKA ET AL.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-18 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *6-9,11,12,14-16,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,10,13,17,18 and 22-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response filed on 03/02/2009 is acknowledged.

2. Claims 1-3 and 5-18 and 20-25 are pending.

3. Claims 6-9, 11-12, 14-16 and 20-21 stand withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a nonelected species.

4. Claims 1-3, 5, 10, 13, 17-18 and 22-25 are currently under examination as they read on a process for inhibiting allergic disease in humans by aerosol administration.

5. In view of Applican'ts response and 1.132 Declaration by Sandor Sipka filed on 03/02/2009, the following rejections are maintained.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, 5, 10, 13, 17-18 and 22-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Cochran et al. (PTO-892 mailed on 01/29/2008; Reference U) in view of Previte et al. (PTO-892 mailed on 05/16/2007, Reference W) for the same reasons as set forth in the Office Action mailed on 10/02/2008.

Applicant's arguments filed on 03/02/2009 have been fully considered, but are not found persuasive.

Applicant argues:

> "Applicants arguments may be distilled to the following: Cochran fails to teach or suggest at least three essential steps of the instant invention. First, as noted by the Examiner, Cochran uses LPS rather than IR-LPS. Second, Cochran teaches a one-time exposure during development while Applicants teach a continual exposure over a critical developmental period. Third, Cochran teaches application of LPS directly to the subject, whereas Applicants teach indirect exposure by application of IR-LPS to the environment. All of these elements are disclosed by Applicants as critical to the efficacy of the inventive method, yet the Examiner ignores the complete absence of the latter two, and applies Previte, a reference that teaches direct administration of IR-LPS to adult mammals to test for a decrease in toxicity, reporting death of nearly a third of the subjects 6 days after administration (see, e.g. Fig. 3), and "extensive inactivation of antigenic antigenic components with increasing radiation dose (page 1611, second column, line 11-14).
>
> With respect specifically to Previte, Applicants have argued that if it is true that the disclosure of Previte would guide an ordinary practitioner to the use of IR-LPS in the methods of Cochran (as the Examiner asserts), then Cochran himself would have employed IR-LPS since Previte was published 35 years prior to Cochran. However, Applicants note that not only does Previte fail to disclose or suggest the missing elements of administration across a developmental continuum and indirect exposure as the form of administration, Previte actually discloses retention of a degree of lethality upon direct administration to adult mammals that would certainly guide a practitioner away from direct administration to a developmentally immature subject. Yet the Examiner expressly states (please note bolded type on page 3, above) that the motivation for using Previte's IR-LPS in Cochran is specifically because a practitioner would conclude based on the teachings of Previte that it would be safe for children and infants! Applicants respectfully demand to know where in Previte it is expressed or implied that the toxic effects of LPS and the retained toxic effects of IR-LPS are eliminated with respect to direct administration to children, infants, or even adults? In fact, Previte may be construed as supporting the thesis that results as to direct administration include that toxicity is retained, although diminished, and that antigenicity is decreased, although substantial decrease is temperature, dose and time dependent. Indeed, Previte expressly teaches "mean survival time was increased by vaccination with LPS but decreased toward control levels when the LPS had been exposed to 5 or 20Mrad. In general, the percentage of survivors, too, decreased similarly. Previte admits that only mortalities recorded up to day 14 are reported, although inactivation of antigenicity peaks much later" (see, e.g. page 1611 second column).
>
> The Examiner continues to stand firm on the position that because IR-LPS is the active, therefore all effects on the subjects are inherent. In taking this position, though, the Examiner fails to consider the distinguishing impact of the route of administration. There is simply no way for the Examiner to conclude that the two methods are identical with respect to toxicity of the active, antigenicity of the active, or with respect to achieving the target outcome. Applicants note that Previte supports this since Previte discloses

full single dosing by direct administration which results in toxicity to a relatively high percentage of subjects, whereas the instant inventive methods rely on passive dosing over a development period by misting the environment without toxic effect. When entering the subject noninvasively and passively via breathing it is clear that parameters such as toxicity and antigenicity are altered.

Applicants have repeatedly argued that a differential effect also exists with respect to exposure to LPS versus IR-LPS and resulting impact on the developing immune system and later immune responsiveness. The Examiner counters that (1) this effect is of no moment since the motivation to combine is based on decreased toxicity so that it would be obvious to use IR-LPS in the methods of Cochran because it would be "safe for infants and children". As set forth in detail above, Applicants respectfully assert this argument as preposterous. The methods of both references involve direct administration of single doses. As disclosed by Previte this results in a completely unacceptable level of toxicity despite irradiation of the LPS. One cannot fathom a method being considered "safe" for infants where the survival rate is 7/10 at six days post- challenge, a result disclosed as a good result by Previte (see Fig. 3, e.g.). Further, Applicants submit that bioequivalence simply does not exist where considering single high invasive dosing versus virtually constant low-level passive exposure and that this would be readily understood by a person of ordinary skill in the art. (2) The Examiner asserts that Applicants have argued but failed to provide any evidence of an unpredicted or heretofore unknown differential impact of IR-LPS over LPS (see, e.g. October 2 Office Action, page 13, third full paragraph).

Applicants therefore submit the Declaration submitted herewith and attested to by inventor Sandor Sipka, M.D. Ph.D. and executed on February 23, 2009. In the Declaration Dr. Sipka testifies as to experimental protocols and results relating to testing the difference in the *in vivo* immunomodulatory effects of IR-LPS versus LPS when administered in accordance with the instant invention (passively as a mist sprayed into the environment). As stated by Dr. Sipka, the results clearly demonstrate that "prolonged pretreatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS" (page 3, paragraph 6).

Hence, Applicants submit that even in the event the Examiner maintains the position that a prima facie case exists on the basis of the reference, the Declaration constitutes secondary evidence of nonobviousness since it clearly demonstrates that specifically with respect to the methods of the instant invention, IR-LPS yields unexpectedly superior results.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka,* 490 F.2d 981,180 U.S.P.Q. 580 (CCPA 1974). In order to render a claimed invention obvious, the prior art must enable one skilled in the art to make and use the claimed invention, *Motorola, Inc. v. Interdigital Tech. Corp.,* 43 U.S.P.Q.2d 1481, 1489 (Fed. Cir. 1997). The combined references fail to teach or suggest methods comprising more than a single treatment applied directly to the subject, whereas the method defined by the instant claims require a duration of passive administration/exposure by, e.g. repeated administration across a maturation period of the subject with application to the subject's living environment. While Cochran posits that certain data "appears" consistent with the original hypothesis that LPS confers a protective effect against allergic asthma, Cochran admits that the actual results fail to yield a disrupting in the Thl/Th2 balance, a disruption that Cochran teaches is implicated in restoring a normal Thl/Th2 balance to protect against the development of asthma. The secondary reference, Previte, which teaches single high doses of IR-LPS to adult subjects to investigate the relations between irradiation and retention of lethality and antigenicity, fails to overcome the deficiencies of Cochran. Previte actually discloses an unacceptably high death rate in subjects (a good result being 3 deaths out of 10 subjects) and that components of antigenicity relating to long terms adaptations of the immune system (such as that which would be necessary to protect against development of asthma) may be destroyed by the levels of radiation needed for detoxification sufficient to eliminate lethality. Hence, at least two important elements of the instant invention are completely unaddressed by the combined references: the passive administration and the continual administration across a developmental period.

Moreover, there is no motivation in either reference to combine the teachings, since Previte is directed to treatment of adult subjects and teaches retention of an unacceptable degree of toxicity for medical uses, and further teaches against uses of IR-LSP for eliciting an adaptive immune response. Finally, importation of the IR-LPS of Previte into the Cochran protocol still fails to enable the present methods, which require more than a single exposure during a maturation period of the developing mammal and administration by application to the environment of the mammal."

For these reasons Applicants submit that instant claims 1-3, 5, 10, 13, 17-18 and 22-25 are nonobvious and patentable under 35 U.S.C. 103(a) over Cochran in view of Previte. Reconsideration is respectfully requested. "

The 1.132 declaration by Sandor Sipka states:

1. He is a co-inventor of and familiar with the present application Serial No. 10/651,136 filed on August 28, 2003, is familiar with the Official Action dated October 2, 2008, and the references cited therein, specifically, Cochran et al, "Influence of Lipopolysaccharide Exposure on Airway Function arid Allergic Responses in Developing Mice," Pediatric Pulmonology, 34:267-277 (2002), Previte et al, "Detoxification of Salmonella typhimurium Lipopolysaccharide by Ionizing Radiation," Journal of Bacteriology, 93(5):1607-1614 (1967), and Khan et al, "Functional and immune response to lipopolysaccharide and allergens in developing mice," Pediatric Research, 51:474A, (2002).

2. He holds the position of Chief of the Regional Immunological Laboratory, Third Department of Internal Medicine, University of Debrecen, Research Center for Molecular Medicine, Medical and Health Science Center, Debrecen, Hungary and is knowledgeable in the art of immunology.

3. The present invention is based on the discovery of a unique immune response elicited by irradiation-detoxified (IR) lipopolysaccharide (LPS) and the use of the IR-LPS in a method of decreasing development of allergic asthma by exposing a neonatal o1" immature mammal to the/R-LPS. To demonstrate the unexpected and surprising results of the present methods, the experiments described herein were conducted under his direction and control to test whether IR-LPS exhibits characteristics different from native LPS with respect to in vivo immunomodulatory allergy-prevention.

4. As part of a pre-treatment regimen, water and equal concentrations of native LPS mad IR-LPS were sprayed for 8 weeks into the cages of infant mice (age at onset =6 weeks, Balb/c mice). At the end of the pretreatrnent period the animals were sensitized by two intraperitoneal injections of 150 μg ragweed allergen (RWE). On day 11 following the sensitization treatment they were challenged with 100 μg RWE. Three days later the cell counts (macrophages and neutrophils/ml) of bronchial lavage (BAL) were measured as well as the serum concentrations of TNFα, a Thl type cytokine (determined by ELISA). The concentrations of cytokines IL-4 and IL-5 (a Th2 cytokine) were also measured but concentrations for all but IL-5 in the IR-LPS group were below detection limits.

5. The measured results were as follows: Table 1. The average number of inflammatory neutrophil granulocytes in the bronchial lavage fluid of ragweed sensitized mice after allergen challenge following daily pre- treated with water (H20), LPS or IR-LPS sprays for 8 weeks.

6. The results set forth in time above Table 1 demonstrate that during the allergic reaction to ragweed, the number of inflammatory neutrophils was significantly decreased in the group of mice treated with IR-LPS ($p = 0.02$) compared to those treated with either H2O spray or native LPS. The results set forth in Table 2 demonstrate that during the ragweed- specific allergic reaction the serum level of TNFα (Thl type cytokine) was increased significantly by 3.56 fold ($p = 0.001$) compared to the controls (16.31/4.58=3.56). However the effect of native LPS was only 1.66 fold (7.60/4.58=1.66). These results

illustrate a striking difference between the in vivo immunomodulatory effects of IR-LPS and native LPS on macrophage and neutrophil numbers. This indicates that the prolonged pre-treatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS. Furthermore, it is clear that IR- LPS caused a significant increase in the serum concentration of TNFα compared to LPS. It is his opinion that the surprisingly marked difference between the in vivo effects of IR-LPS and native LPS is due to their differing antigenic character which acts on the immunomodulatory Thl type cells having antigen-specific T cell receptors. It is further his opinion that irradiation of LPS with 150 kGY 60Co-gamma ray results in production or revelation of a new or formerly hidden antigenic determinant(s) in the components of IR-LPS lending the altered and different antigenic character as clearly demonstrated in this study.

7. The Surprisingly superior effect of IR-LPS over native LPS in protecting against the development of a hyperimmune response to an allergen is neither taught nor suggested by any of the prior art cited in the Official Action as noted above or otherwise known to me. Thus, none of this prior art, alone or in combination, suggests any benefit of using IR-LPS, particularly as compared with native LPS, in a method of decreasing development of allergic asthma. Accordingly, none of this prior art, alone or in combination, suggests a method of decreasing development of allergic asthma by exposing a neonatal or immature mammal to IR-LPS.

8. He further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or may patent issued thereon. "

It is the Examiner's position that Applicant is arguing limitations that are not present in the claims when they argue that "Applicants teach a continual exposure over a critical developmental period" and that "Applicants teach indirect exposure by application of IR-LPS to the environment." The claims are not limited to methods comprising these two limited assertions. "At least weekly administration during maturation of the mammal" is not equivalent to "continual exposure over a critical developmental period" and "to a living environment of the mammal" is not equivalent to "indirect exposure by application of IR-LPS to the environment" as defined by the specification. The claims are given their broadest reasonable interpretation, given the definitions and disclosure in the specification. The Examiner's interpretation of the claims in light of the specification makes the combination of the two instant references obvious to arrive at the instant claimed invention. But, even if that wasn't the case, these two limitations are directed

to dosing which is something that is well-known to skilled artisans and optimal dosing procedures are art-recognized results-effective variables which are well within the purview of those of ordinary skill in the art to determine.

Applicant's argument that "Applicants have argued that if it is true that the disclosure of Previte would guide an ordinary practitioner to the use of IR-LPS in the methods of Cochran (as the Examiner asserts), then Cochran himself would have employed IR-LPS since Previte was published 35 years prior to Cochran." is not persuasive. The Examiner has provided sound reasoning for combining the teachings of the references. The fact that the authors of the reference did not combine the teachings is not relevant to the instant rejection and is an unpersuasive argument for obviousness rejections in general.

In response to Applicant's assertion that "Applicants respectfully demand to know where in Previte it is expressed or implied that the toxic effects of LPS and the retained toxic effects of IR-LPS are eliminated with respect to direct administration to children, infants, or even adults?" It is the Examiner's position that Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non-irradiated LPS. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is again noted that LPS is fully toxic and is being used medically in both the Previte et al. and Cochran et al. references.

It is noted that Applicants assert evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. However, such evidence has not been brought forth in the instant application that is commensurate in scope with the claims, including the instant declaration by Sandor Sipka filed on 03/02/2009. The declaration provides evidence of the effect of irradiated LPS given daily in aerosol form on the development of inflammatory neutrophil granulocytes, TNF-α and IL-5 in ragweed sensitized young mice. The results set forth in the declaration are neither surprising nor are they commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly. Applicants are encouraged to submit additional data that is commensurate in scope with the claimed invention to demonstrate surprising or unexpected results. Neither the declaration of Sandor Sipka nor the arguments by Applicants filed on 03/02/2009 are persuasive to overcome the instant rejection. Accordingly, the rejection stands for reasons of record.

8. Claims 1-3, 5, 10, 13, 17-18 and 22-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Khan et al. (PTO-892 mailed on 01/29/2008, Reference V) in view of Previte et al. (PTO-892 mailed on 05/16/2007, Reference W) for the same reasons as set forth in the Office Action mailed on 10/02/2008.

Applicant's arguments filed on 03/02/2009 have been fully considered, but are not found persuasive.

Applicant argues:

"Applicants' prior arguments may be summarized as follows: (1) Khan specifically notes that treatment with LPS did not affect allergen-induced airway hyperresponsiveness (AHR), and teaches that "airway exposure to LPS produces transient AHR and inflammation in developing mice and **does not appear to influence functional and immune responses induced by subsequent allergen sensitization"** (see Poster Board 219); (2) Khan is part of the same research team as Cochran and published these findings as inconsistent with the results/conclusions of Cochran, in particular with respect to impact on subsequent allergen sensitization; (3) Khan expressly teaches that LPS does not appear to influence the very responses sought to be elicited by the instant invention; (4) Previte fails to teach or suggest the immunostimulatory properties of irradiated LPS that underpin the instant inventive methods; and (5) Previte teaches retention of unacceptable morbidity at IR levels within the scope of the instant invention and suggests that the level of irradiation necessary to effectively detoxify LPS results in destruction of the components of antigenicity that may be related to eliciting a long term adaptive immune response.

Applicants further argue that a person of ordinary skill in the art seeking methods to decrease development of allergic asthma would be discouraged from employing the IR-LPS of Previte into the protocols of Cochran or Khan because Previte teaches a single relative high dose to adult rats which results in an unacceptably high death rate among the subjects. (Although the Examiner objects that Applicants may not define what is "acceptable", Applicants contend that a positive death rate predictably due to the treatment, as disclosed by Previte for IR levels within the scope of the instant invention, would be universally understood as unacceptable and that no expert opinion need be procured to attest to this understanding). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. *See Ruiz v. A.B. Chance Co.,* 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000)."

Applicants argue that a person of ordinary skill in the art would not be guided by the teachings of Previte to use IR-LPS in the methods of Khan based on the motivation assessed by the Examiner - that it would be safe for children and infants. Indeed, Previte fails to consider administration to immature subjects and notes unacceptably high death rates among adult subjects where IR doses are low enough for retention of antigenicity. The Examiner argues that regardless of this, all primary references teach use of non-irradiated LPS and Applicants have failed to demonstrate any unexpected difference between LPS and IR-LPS specifically with respect to the targeted outcome of reducing. Hence, Applicants submit the attached Declaration by inventor Sipka attesting to the differential and unexpected impact of IR-LPS over LPS in in vivo studies testing assessing the targeted outcome of allergy prevention."

The 1.132 declaration by Sandor Sipka states:

1. He is a co-inventor of and familiar with the present application Serial No. 10/651,136 filed on August 28, 2003, is familiar with the Official Action dated October 2, 2008, and the references cited therein, specifically, Cochran et al, "Influence of Lipopolysaccharide Exposure on Airway Function arid Allergic Responses in Developing Mice," Pediatric Pulmonology, 34:267-277 (2002), Previte et al, "Detoxification of Salmonella typhimurium Lipopolysaccharide by Ionizing Radiation," Journal of Bacteriology, 93(5):1607-1614 (1967), and Khan et al, "Functional and immune response to lipopolysaccharide and allergens in developing mice," Pediatric Research, 51:474A, (2002).

2. He holds the position of Chief of the Regional Immunological Laboratory, Third Department of Internal Medicine, University of Debrecen, Research Center for Molecular Medicine, Medical and Health Science Center, Debrecen, Hungary and is knowledgeable in the art of immunology.

3. The present invention is based on the discovery of a unique immune response elicited by irradiation-detoxified (IR) lipopolysaccharide (LPS) and the use of the IR-LPS in a method of decreasing

development of allergic asthma by exposing a neonatal o1" immature mammal to the/R-LPS. To demonstrate the unexpected and surprising results of the present methods, the experiments described herein were conducted under his direction and control to test whether IR-LPS exhibits characteristics different from native LPS with respect to in vivo immunomodulatory allergy-prevention.

4. As part of a pre-treatment regimen, water and equal concentrations of native LPS mad IR-LPS were sprayed for 8 weeks into the cages of infant mice (age at onset =6 weeks, Balb/c mice). At the end of the pretreatrnent period the animals were sensitized by two intraperitoneal injections of 150 μg ragweed allergen (RWE). On day 11 following the sensitization treatment they were challenged with 100 μg RWE. Three days later the cell counts (macrophages and neutrophils/ml) of bronchial lavage (BAL) were measured as well as the serum concentrations of TNFα, a Thl type cytokine (determined by ELISA). The concentrations of cytokines IL-4 and IL-5 (a Th2 cytokine) were also measured but concentrations for all but IL-5 in the IR-LPS group were below detection limits.

5. The measured results were as follows: Table 1. The average number of inflammatory neutrophil granulocytes in the bronchial lavage fluid of ragweed sensitized mice after allergen challenge following daily pre- treated with water (H20), LPS or IR-LPS sprays for 8 weeks.

6. The results set forth in time above Table 1 demonstrate that during the allergic reaction to ragweed, the number of inflammatory neutrophils was significantly decreased in the group of mice treated with IR-LPS ($p = 0.02$) compared to those treated with either H2O spray or native LPS. The results set forth in Table 2 demonstrate that during the ragweed- specific allergic reaction the serum level of TNFα (Thl type cytokine) was increased significantly by 3.56 fold ($p = 0.001$) compared to the controls (16.31/4.58=3.56). However the effect of native LPS was only 1.66 fold (7.60/4.58=1.66). These results illustrate a striking difference between the in vivo immunomodulatory effects of IR-LPS and native LPS on macrophage and neutrophil numbers. This indicates that the prolonged pre-treatment of the environment of infant mice with IR-LPS acts to prevent the intensity of ragweed specific allergic reaction differentially when compared to native LPS. Furthermore, it is clear that IR- LPS caused a significant increase in the serum concentration of TNFα compared to LPS. It is his opinion that the surprisingly marked difference between the in vivo effects of IR-LPS and native LPS is due to their differing antigenic character which acts on the immunomodulatory Thl type cells having antigen-specific T cell receptors. It is further his opinion that irradiation of LPS with 150 kGY 60Co-gamma ray results in production or revelation of a new or formerly hidden antigenic determinant(s) in the components of IR-LPS lending the altered and different antigenic character as clearly demonstrated in this study.

7. The Surprisingly superior effect of IR-LPS over native LPS in protecting against the development of a hyperimmune response to an allergen is neither taught nor suggested by any of the prior art cited in the Official Action as noted above or otherwise known to me. Thus, none of this prior art, alone or in combination, suggests any benefit of using IR-LPS, particularly as compared with native LPS, in a method of decreasing development of allergic asthma. Accordingly, none of this prior art, alone or in combination, suggests a method of decreasing development of allergic asthma by exposing a neonatal or immature mammal to IR-LPS.

8. He further declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or may patent issued thereon. "

It remains the Examiner's position that Khan need not demonstrate results which demonstrate effective treatment, as alleged by Applicant. The reference need not teach prevention or permanent efficacious treatment for airway hyperresponsiveness in order to be used as a reference. The reference is being relied on for its specific teachings, namely the administration of LPS to neonatal or immature mammals to decrease development of allergic asthma.

It also remains the Examiner's position that Previte teaches that lethality is decreased in general and that is all that is required of the reference to make the argument that when giving LPS to children irradiated LPS would be preferred since it exhibits decreased lethality over non-irradiated LPS. One of ordinary skill in the art would have been motivated to use the irradiation detoxified lipopolysaccharide of Previte et al. in process for decreasing allergic asthma of Khan et al. because the process should be safer and with less toxic effects for use in infants and children. Previte et al. teaches that LPS can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity. Applicant's assertions that lethality is still higher than what would be considered acceptable in a treatment and that Previte teaches an unacceptable degree of toxicity for medical uses is unpersuasive. The reference teaches that toxicity is decreased and that teaching alone provides motivation to use irradiated LPS in place of LPS. It is again noted that LPS is fully toxic and is being used medically in both the Previte et al. and Khan et al. references.

It is noted that Applicants assert evidence of an unpredicted and heretofore unknown differential impact of IR-LPS over LPS. However, such evidence has not been brought forth in

the instant application that is commensurate in scope with the claims, including the instant declaration by Sandor Sipka filed on 03/02/2009. The declaration provides evidence of the effect of irradiated LPS given daily in aerosol form on the development of inflammatory neutrophil granulocytes, TNF-α and IL-5 in ragweed sensitized young mice. The results set forth in the declaration are neither surprising nor are they commensurate in scope with the claims, which are directed to a method of decreasing development of allergic asthma in neonatal or immature mammals by administration to a living environment of the mammal at least weekly. Applicants are encouraged to submit additional data that is commensurate in scope with the claimed invention to demonstrate surprising or unexpected results. Neither the declaration of Sandor Sipka nor the arguments by Applicants filed on 03/02/2009 are persuasive to overcome the instant rejection. Accordingly, the rejection stands for reasons of record.

9. No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 12, 2009
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